REMARKS

The Official Action of February 22, 2001, has been carefully considered and reconsideration of the application as amended is respectfully requested.

Claim 21, directed to the compound, has been cancelled. The claims remaining are directed to a method for treatment of malaria comprising administering the compound of formula (I) to an animal in "a therapeutically effective amount" for the treatment. The recitation "therapeutically effective amount" requires not only that the recited compound be effective to kill malarial parasites, but also that it not be toxic to the animal in the recited amount.

As discussed in Applicants' amendment dated December 5, 2000, the evidence of record in the specification and in the literature references of record establish a long-felt need for a primaquine derivative that has anti-malarial activity and yet overcomes the longstanding problem posed by the toxicity of the prior art compound. The Examiner has respectfully not addressed the evidence of unsolved need, which Applicants respectfully assert must be considered before a conclusion of obviousness can be reached (see, for example, *In re Piasecki*, 223 USPQ 785, 790 (Fed. Cir. 1984): "Evidence of secondary considerations may often be the most probative and cogent evidence in the record.").

The Examiner, while acknowledging that Applicants have recited the various advantages of the claimed compound over primaquine, has contended that Applicants have allegedly not recited advantages over the prior art compound. However, Applicants respectfully note that the evidence of unsolved need of record subsumes the prior art compounds. For example, the

Saxena et al article cited at page 3 of Applicants' Amendment dated December 5, 2000, states in pertinent part: "Primaquine, the most important member of the 8-aminoquinoline group, is the only drug which is used in the treatment of relapsing malaria, in spite of its known toxic effects on the host system . . . ." In other words, the Saxena article, which was published 55 years after issuance of the Andersag patent, does not consider only primaquine as failing to solve a longstanding problem, but considers all of the prior art compounds (among which primaquine is considered to be the most prominent) as failing to solve the problem.

Although Applicants believe that the evidence of secondary considerations would be sufficient to overcome any alleged *prima facie* case of obviousness based upon the Andersag reference, Applicants also respectfully submit that the reference is not sufficient even to set forth a *prima facie* case for alleged obviousness. This is because, even assuming for the sake of argument that one of ordinary skill in the art would be motivated to modify the compound of Andersag Example 11 as contended by the Examiner, there still would not be a reasonable expectation of success in practicing the claimed method as would be required to establish a *prima facie* case of obviousness (see MPEP Section 2143). In this connection, Applicants respectfully call the Examiner's attention to the specification at pages 6 - 9, wherein the therapeutic activity and the toxicity of primaquine and its metabolites are discussed. The specification shows clearly the unpredictability in this art and the effect of small structural changes on the biological activity of primaquine and its derivatives. Given this unpredictability, Applicants respectfully submit that one of skill in the art could not have had even a reasonable expectation from Andersag that the claimed compounds (a) could be safely administered to a patient in any dosage, and (b) could be effective in treating the patient against malaria (see *Ortho Pharmaceutical Corp. v. Smith*, 22, USPQ 2d 1119, 1125 (Fed. Cir. 1992)).

The above is especially true in view of the limited disclosure in Andersag and the contradictory disclosure of the prior art as a whole. In this connection, it is axiomatic that each prior art reference must be evaluated as an entirety, and all of the prior art must be evaluated as a whole (see, e.g., *In re Evanega*, 44 USPQ 2d 1249 (Fed. Cir. 1987)). When considering Andersag as an entirety, it must be recognized that the reference contains only a passing reference to usefulness of the entire class of described compounds in the treatment of malaria. This does not mean, nor would it be taken by those of skill in the art to mean, that each and every compound within the described genus (nor even each and every compound exemplified in the patent) would be useful against malaria parasites. Moreover, the general statement of usefulness in the Andersag reference must be considered in the context of the prior art as a whole. As can be gleaned from the references cited in the specification at pages 6 - 9, and as discussed above, one cannot generalize as to the effectiveness or toxicity of primaquine or its derivatives. Indeed, the prior art when considered as a whole, teaches the opposite, i.e., generalization is impossible. Moreover, the evidence of unsolved need belies any implication that all compounds embraced by the Andersag genus would be useful to treat malaria.

For the reasons discussed above, it is respectfully submitted that the passing reference in Andersag to the usefulness of the genus of compounds described therein could not establish even a reasonable expectation of success with use of the recited compounds in the claimed method. Moreover, to understand the scope of the Andersag reference, it is necessary to understand the terminology involved in treatment of malaria.

(a) A malarial parasite undergoes two distinct cycles of development.

- The asexual stage (in humans) comprises the asexual parasites residing in liver cells and red blood cells. Drugs that kill the parasite at this stage are called anti-malarial or anti-parasitic (Andersag is an example of anti-malarial drug);

- The sexual cycle of parasitic development comprises completely different stages -- gamete, zygote and oocyst. For example, when a non-infected mosquito bites the malaria infected subject, gametocytes are transmitted to the mosquito and transform into gametes and subsequently develop into zygotes/oocysts. Gametocytocidal drugs (such as the compound of the invention) interfere with the development of the parasite at the gamete stage. Thus, treatment with a gametocytocidal drug interrupts the development of gametocytes in the vector/infected patient and therefore blocks the further transmission of malarial parasite.

(b) At the time of the Andersag patent, biological assay of gametocytocidal activity was unknown. The teaching of Andersag is at best interpreted to mean possible efficacy against the asexual erythrocytic stage/liver stage parasites and not to transmission blocking potential of gametocytocidal agents interrupting the development of gametocytes.

(c) It would therefore be incorrect to extrapolate the single passing reference to anti-malarial activity in Andersag to the specific function performed by the primaquine derivative used in the claimed invention.

In view of the above, it is respectfully submitted that the cited art does not set forth even a *prima facie* case for alleged obviousness of the invention as claimed. Moreover, it is respectfully submitted that the evidence of secondary considerations of record would be sufficient to overcome any alleged *prima facie* case. Accordingly, Applicants respectfully submit that the rejections of record have been overcome and that the application is in allowable form. An early

Notice of Allowability is earnestly solicited and is believed to be fully warranted.

Respectfully submitted,

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